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| 10/541,522 | 07/07/2005 | William Brown | 100952-1P US | 2007 |

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| EXAMINER | |
|---|---|
| O'DELL, DAVID K | |

| ART UNIT | PAPER NUMBER |
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| 1625 | |

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|---|---|
| 05/14/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/541,522 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | David K. O'Dell | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,7-10 and 13-23* is/are pending in the application.

4a) Of the above claim(s) *7,9,10 and 14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,13 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**1.** This application is a 371 of PCT/GB04/00099 filed 01/13/2004 and claims priority to SWEDEN 03001054 filed 01/16/2003.

Claims 1-5, 7-10, 13-23 are pending. Claims 7, 9, 10, 14-18 are withdrawn from consideration. Claims 1-5, 8, 13, 19-23 are under examination.

### *Response to Restriction/Election*

2. Applicant's election of group I and the species compound 8 in the reply filed on February 21, 2008 is acknowledged. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP §818.03(a)). This requirement is made FINAL. This application contains claims drawn to a nonelected invention. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under examination:

Group I, , Claims 1-5, 8, 13, 19-23 drawn to compounds and compositions.

### *Information Disclosure Statement*

3. The information disclosure statement (IDS) submitted on October 19, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-5, 8, 13, 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,187,792 OR U.S. 6,455,545, OR WO9828275 in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905 cited on the IDS, in further view of Iddon et. al. "Acetamides of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (benzomorphan), 5,6.7,8,9,10-hexahydro-6,9-methanobenzocyclo-octene, and 6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[b][1]benzothiophene as potential selective opioid analgesics." *Journal of the Chemical Society Perkin Transaction* 1, **1990**, 1091 -1095. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

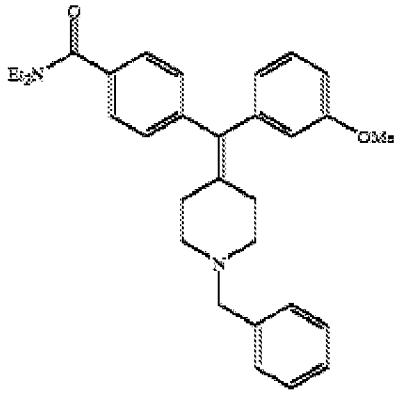
**Determination of the scope and content of the prior art**

***(MPEP 2141.01)***

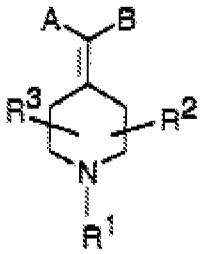
The U.S. 6,187,792 OR U.S. 6,455,545, OR WO9828275 documents all teach a large group of compounds bearing essentially the same piperidinyl-diphenylmethane core. These compounds have the same utility, namely as δ-opioid agonists, selective over the other opioid receptor subtypes. A few examples are shown below:

EXAMPLE 23

Preparation of N,N-Diethyl-4-{(N-benzyl)-3-methoxyphenyl-piperidin-4-ylidene-methyl}-benzamide (compound 37)

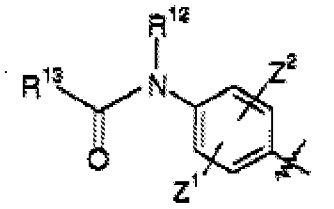


Most compelling is the suggestion of the generic disclosure that reverse amides are preferred substituents as shown below (taken from page 3-4 of WO9828275).



(I)

A is selected from




Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel.....and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905 teaches that while the phenyl ring bearing the dialkylamide group was important for activity, other features in particular the substituents on the other phenyl ring (i.e. the methoxy group of SNC-80) were less sensitive to changes and that preparing compounds with such modifications would likely be the right place to look for more potent compounds. In the author's own words:

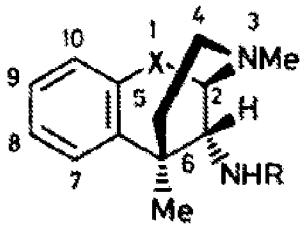
"Initial SAR studies1[5] around SNC-80 indicated that the 4-N,N-diethylaminocarbonyl group is a key structural feature, but neither the methoxy group, the allyl group, nor the two methyl groups on the piperazine were essential for high affinity at the δ opioid receptor that does not bear the is a site ripe for modification." (pg. 2895 column 2)

"The opioid receptor binding affinity, selectivity, and agonist potency of the target compounds **6** are listed in Table 1, and those of SNC-80, diarylmethylpiperazine **4**, and diarylmethylpiperidine **5** are also included for comparison. As compared to SNC-80 [$\delta$– $IC_{50}$ ) 1.31 nM; μ/δ =245; $\kappa/\delta$ = 1890 (*K*i ) 4 nM; $\mu/\delta$=990 on rat brain membranes)[18]], compound **6f** displayed similar binding affinity [$IC_{50}$ ) 1.56 nM (*K*i ) 5 nM; $\mu/\delta$ > 1200 on rat brain membranes)18] on $\delta$ receptors but an improved selectivity over $\mu$ and $\kappa$ receptors (μ/δ = 3370; $\kappa/\delta$ > 6410). **6a**, a derivative of **6f** without the 3-MeO group on the phenyl ring, even further increased selectivity as a result of improved $\delta$ -affinity (IC50 ) 0.87 nM; μ/δ= 4370; $\kappa/\delta$ = 8590). **Considerable variation is possible in the nature of the substitution on the phenyl ring, and this can lead to some highly potent $\delta$ agonists**." (pg. 3897 column 2, Results and Discussion)

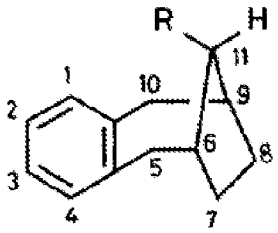
Iddon et.al teach that in the field of opiod receptor ligands the conversion of amino group to amide is a well-known and desirable modification:

---

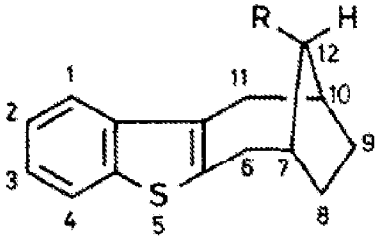
Separation of the desirable pain-killing properties of the opioid analgesics from their less desirable side-effects, such as addiction, respiratory depression, and tolerance, has become an achievable goal following recognition that some compounds can exhibit specificity for the different opioid receptors.[1] Reports (*e.g.* refs. 2 and 3) that opioid activity has been observed with some amides of diverse chemical structure prompted us to synthesize an amide derivative (**1**) of benzomorphan and to convert the oximes whose syntheses are described in our preceding paper[4] into the corresponding amides, (**3**), (**6**), and (**10**).



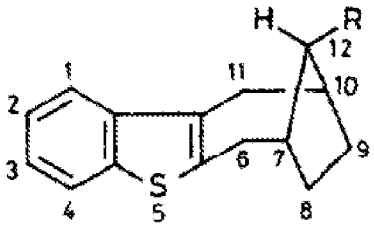

(1) R = Ac
(2) R = H




(3) R = NHAc
(4) R = $NH_2$
(5) R = NHEt



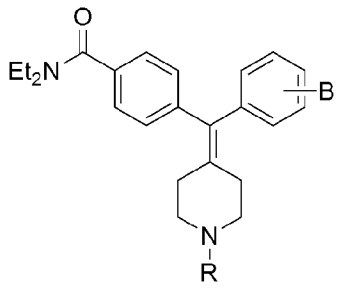

(6) R = NHAc
(7) R = $NH_2$
(8) R = NHEt
(9) R = OH




(10) R = NHAc
(11) R = $NH_2$
(12) R = NHEt

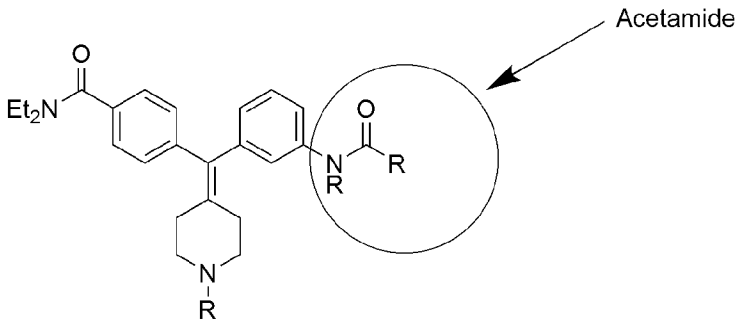
***Ascertainment of the difference between the prior art and the claims***

It is clear that the prior art differs only in the substitution of the acetamide group on one of the phenyl rings, at least where $R_1$ is phenyl of the instant case. This relationship is shown graphically in Figure 1.




B = $NO_2$, halogen, SMe, OMe, (C=O)Me, alkyl, amino, $CF_3$

The teaching of the Prior art.




The instant claims

Figure 1. The difference between the prior art and the instant claims.

***(MPEP 2141.02)***

**Finding of prima facie obviousness**

***Rational and Motivation***

***(MPEP 2142-2143)***

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of U.S. 6,187,792 OR U.S. 6,455,545, OR WO9828275 to produce the instant invention. The experienced Ph.D. synthetic organic chemist, who would

make Applicants' compounds, would be motivated to prepare these compounds by the suggestion of Wei et. al. who stated that "Considerable variation is possible in the nature of the substitution on the phenyl ring, and this can lead to some highly potent $\delta$ agonists." The variation of the instant case was a known modification as shown by the generic teaching of the WO document, and the teaching of Iddon.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "$C_6$-$C_{10}$ aryl" and "$C_2$-$C_6$ heteroaryl". From the specification we know that the terms "aryl" and "heteroaryl" are meant to describe aromatic compounds.

> The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms.
>
> The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (e.g., 4n + 2 delocalized electrons).

Presumably "$C_6$-$C_{10}$ aryl" is meant to include compounds having 7, 8, & 9 carbon atoms, and "$C_2$-$C_6$ heteroaryl" includes compounds having 2, 3, & 4 carbon atoms however such compounds cannot be aromatic and thus conflict with the definition. For a discussion of aromaticity see Jones, M. *Organic Chemistry* Norton: New York, 1997, pgs. 578-591. The examiner believes this is meant to be phenyl and naphthyl for $C_6$-$C_{10}$ aryl and perhaps something else entirely for "$C_2$-$C_6$ heteroaryl". A clarification and appropriate correction is required.

### *Claim Rejections - 35 USC § 112 1st paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2 , 8, 13, 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds corresponding to Formula (I) or (III),

it does not reasonably provide enablement for the long list of potential groups $R_1$. In particular the prophetic heterocycles of "$C_{2-6}$heteroaryl" nor the optional substituents on $R_2$, $R_3$, $R_4$ & $R_5$. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

> ***(A) The breadth of the claims;***
> ***(B) The nature of the invention;***
> ***(C) The state of the prior art;***
> ***(D) The level of one of ordinary skill;***
> ***(E) The level of predictability in the art;***
> ***(F) The amount of direction provided by the inventor;***
> ***(G) The existence of working examples; and***
> **(H) The quantity of experimentation needed to make or use the invention**

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

**(A) The breadth of the claims:** The claims are very broad encompassing a variety of heterocycles, bearing multiple substitutions **(B) The nature of the invention:** This is a medicinal chemistry invention requiring the synthesis of compounds and these compounds must have the utility of treating pain or at least as ligands at opioid receptors. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing medicinal chemist. The following Wand factors will be discussed in detail below: **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:**

While little information was given in the specification, the examiner would like to point the applicant's attention to the tables 1 & 2 (pg. 24), which reveal the level of activity at the δ, κ, and μ opioid receptors for only nine compounds. (**F**) & (**G**)

Table 1

| Compd. # | Human δ (nM) | | | Human κ (nM) | Human μ (nM) | RAT BRAIN (nM) | |
|---|---|---|---|---|---|---|---|
| | $IC_{50}$ | $EC_{50}$ (high) | %EMax (high) | $IC_{50}$ | $IC_{50}$ | $EC_{50}$ | %EMax |
| 3-4 | 0.34-0.59 | 1.46-2.65 | 95-98 | 2470-8000 | 344-368 | 7.2-15.8 | 126-137 |

Table 2

| Compd. # | Human δ (nM) | | | Human κ (nM) | Human μ (nM) |
|---|---|---|---|---|---|
| | $IC_{50}$ | $EC_{50}$ (low) | %EMax (low) | $IC_{50}$ | $IC_{50}$ |
| 1-2, 5-9 | 0.19-1.49 | 15.7-274 | 80-112 | 5828-9074 | 106-4441 |

In order to further clarify as to what activity at these opioid receptors is and to make the record extremely clear that that examiner is not taking official notice of this fact, but rather that this conclusion is based on the objective statements of those in the art, the following discussion and publications are submitted that describe exactly what is meant by "activity" or "inactivity".

It is an art recognized phenomenon in pharmacology that compounds having activity above a certain threshold are inactive, meaning that they do not have that activity. In binding assays (like those of the instant specification) the general threshold is 10 uM or 10,000 nM.

At the very same receptors of the instant case Calo et. al. *British Journal of Pharmacology* **2002**, 136, 303 - 311.

> "UFP-101 **was essentially inactive at DOP and MOP sites, where about 30% inhibition of [3H]-diprenorphine binding was observed at 10 μM UFP-101**."

And Chang et. al. MOLECULAR PHARMACOLOGY, **1984**, *26*, 484-488, describing opioid ligands:

> "When guinea pig brain membrane in the presence of ιz- and #{244}-ligands is used as K-sites source and [3H] diprenorphine as labeled ligand, EKC is a potent competitor but DADLE is **virtually inactive and the IC50 value is about 10 μM** (Fig. 3). Again, these data are consistent with the data reported by Corbett et al. (24) that **DADLE is virtually inactive as a K-ligand.**"

And Erchegyi et. al. *Journal of Medicinal Chemistry* **2003,** *46,* 5587-5596.

"**Binding affinity, on the other hand, was completely lost at all receptors in 7 and 8,** which indicates that the threo configuration is favored over the erythro configuration. Our findings are in agreement with the results of Huang et al., who found that only the (2*R*,3*S*)- and (2*S*,3*R*)-*â*-MeTrp isomers were allowed at position 8 in the potent c[Pro6-Phe7-DTrp8-Lys9-Thr10-Phe11] SRIF analogue."

Table 3. $sst_{1-5}$ Binding Affinities ($IC_{50}$, nM) of $sst_4$-Selective Analogues and Control Peptides

| | $IC_{50}$ (nM)[a] | | | | |
|---|---|---|---|---|---|
| no. | $sst_1$ | $sst_2$ | $sst_3$ | $sst_4$ | $sst_5$ |
| 1 | 3.8 ± 0.4 (25) | 2.7 ± 0.2 (25) | 4.9 ± 0.5 (24) | 3.1 ± 0.2 (24) | 2.9 ± 0.2 (24) |
| 2 | 607 ± 168 (3) | 173 ± 41 (3) | 6.7 ± 1.9 (3) | 41 ± 19 (3) | 34 ± 10 (3) |
| 3 | >1000 (2) | 57 (63; 51) | 3.4 (3.2; 3.5) | 1.4 (1.6; 1.1) | 13 (14; 13) |
| 4 | >1000 (2) | 24 (25; 23) | 3.1 (2.9; 3.2) | 1.2 (0.95; 1.5) | 9 (9.5; 8.4) |
| 5 | 410 (300; 520) | 30 (30; 30) | 18 (22; 14) | 2.2 (4; 0.35) | 17.5 (18; 17) |
| 6 | >1000 (4) | 110 ± 15 (3) | 600 ± 255 (3) | 2.1 ± 0.6 (4) | 147 ± 3.3 (4) |
| 7 | >1000 (2) | >1000 (2) | >10K (2) | 105 (160; 50) | >1000 (2) |
| 8 | >10K (1) | >10K (1) | >1000 (1) | >1000 (1) | >10K (1) |
| 9 | >1000 (2) | 102 (79; 125) | 186 (130; 241) | 8.7 (8; 9.4) | 101 (70; 131) |
| 10 | >10K (2) | 575 (400; 750) | >1000 (2) | 6.9 (6.5; 7.2) | >1000 (2) |
| 11 | 545 ± 122 (4) | 12 ± 2 (4) | 14 ± 3 (4) | 0.53 ± 0.04 (3) | 27 ± 5.5 (3) |
| 12 | >10K (6) | 339 ± 103 (6) | 664 ± 81 (5) | 3.5 ± 0.5 (5) | 668 ± 86 (6) |
| 13 | >1000 (3) | 22 ± 16 (3) | 61 ± 47 (3) | 12 ± 8.6 (3) | 152 ± 93 (3) |
| 14 | >10K (3) | 673 ± 368 (3) | 697 ± 118 (3) | 21 ± 2.7 (3) | >1000 (3) |
| 15 | >1000 (2) | 304 (150; 258) | 171 (98; 244) | 9.8 (8; 11.5) | 127 (170; 83) |
| 16 | >1000 (2) | 474 (420; 527) | 595 (340; 850) | 61 (42; 79) | >1000 (2) |
| 17 | >1000 (3) | 16 ± 11 (3) | 12 ± 8 (3) | 9.2 ± 5 (3) | 47 ± 20 (3) |
| 18 | >1000 (4) | 557 ± 131 (3) | 325 ± 84 (4) | 11.8 ± 3 (3) | 700 ± 200 (3) |
| 19 | 778 ± 103 (3) | 26 ± 7.4 (3) | 9.7 ± 2.2 (3) | 1.8 ± 0.3 (3) | 23 ± 16 (3) |
| 20 | >10K (4) | >1000 (3) | >1000 (3) | 30 ± 5.1 (4) | >1000 (3) |
| 21 | >1000 (4) | >10K (4) | >10K (4) | 4.2 ± 1.9 (3) | >10K (4) |

[a] The $IC_{50}$ values (nM) were derived from competitive radioligand displacement assays reflect the affinities of the analogues for the cloned human somatostatin receptors using the nonselective $^{125}$I-[Leu$^8$,DTrp$^{22}$,Tyr$^{25}$]SRIF-28 as the radioligand. Mean value ± SEM when $N \geq 3$ (shown in parentheses). In other cases, values are listed in parentheses.

And Kruzsynski et. al. *Journal of Peptide Research* **2005**, 66, 125-131: "These two compounds were weak l-antagonists in the GPI assay and **were inactive in the MVD assay** (Tables 2 and 3)." [referring to compounds 4 and 5]

*Table 3.* **GPI and MVD assay of endomorphin-2 analogs**

| | | GPI | | MVD | |
|---|---|---|---|---|---|
| Peptide number | Sequence | $IC_{50}$ (nM)[a] | $K_e$ (nM)[a,b] | $IC_{50}$ (nM)[a] | MVD/GPI $IC_{50}$ ratio |
| 1 | Tyr-Pro-Phe-Phe-$NH_2$ (endomorphin-2) | 7.71 ± 1.47 | | 15.3 ± 1.6 | 1.98 |
| 2 | Tyr-Pro-Phe-1-Nal-$NH_2$ | 1130 ± 240 | | >10 000 | |
| 3 | Tyr-Pro-Phe-2-Nal-$NH_2$ | 150 ± 11 | | 1340 ± 80 ($IC_{50}$)[c] | 8.93 |
| 4 | Tyr-Pro-Phe-D-1-Nal-$NH_2$ | | 1250 ± 40 | >10 000 | |
| 5 | Tyr-Pro-Phe-D-2-Nal-$NH_2$ | | 1260 ± 50 | inactive | |

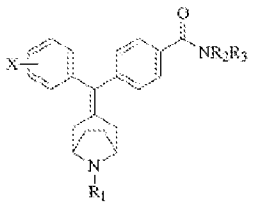
a. Mean of three to five determinations (± SEM).
b. Determined against TAPP (Tyr-D-Ala-Phe-Phe-$NH_2$).
c. Partial agonist (maximal inhibition of electrically induced contractions = 70%).

In a closely related series of compounds, a more modest definition of activity was given, John R. Carson et. al. "N-Alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)phenylmethyl]-benzamides, μ and δ opioid agonists" *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 2113-2116

"The opioid binding affinities of analogues of 3 are shown in Table 1. Interestingly, compound 3 itself was found to embody the optimal structural features within this new structural subclass of l agonists. A secondary amide is necessary for significant l agonist activity. The group attached to the nitrogen of the secondary amide could not deviate far in size from ethyl in order to retain good μ activity. **Methyl, n-propyl, cyclopropyl, and 2-fluoroethyl retained activity but 2-methoxyethyl, N-cyclohexyl, and N-phenyl were inactive.**"

The relevant portion of Table 1 of Carson et. al. is shown below:

Table 1. Opioid receptor binding



| Compd | $R_1$ | $R_2$,$R_3$ | X | Stereochemistry | δ $K_i$, nM | μ $K_i$, nM | μ/δ |
|---|---|---|---|---|---|---|---|
| 2 | 2-Phenethyl | $Et_2$ | H | 1*R*,5*S* | 0.24 | 72 | 305 |
| 3 | 2-Phenethyl | H,Et | H | 1*R*,5*S* | 46.7 | 0.26 | 0.0056 |
| 7 | 2-Phenethyl | $Et_2$ | H | 1*S*,5*R* | 42.1 | 317 | 7.53 |
| 8 | 2-Phenethyl | H,Et | H | 1*S*,5*R* | 4.69 | 7.16 | 1.53 |
| 9 | 2-Phenethyl | H,*n*-Pr | H | *rac* | 22 | 1.6 | 0.073 |
| 10 | 2-Phenethyl | $H_2$ | H | *rac* | 35.9 | 39.6 | 1.1 |
| 11 | 2-Phenethyl | H,*n*-Bu | H | *rac* | 49.3 | 21.7 | 0.44 |
| 12 | 2-Phenethyl | H,Me | H | *rac* | 13 | 0.14 | 0.011 |
| 13 | 2-Phenethyl | H,cycloPr | H | *rac* | 20 | 1.01 | 0.05 |
| 14 | 2-Phenethyl | H,cyclohexyl | H | *rac* | 924 | 717 | 0.78 |
| 15 | 2-Phenethyl | 2-H,methoxy-ethyl | H | *rac* | 103 | 163 | 1.58 |
| 16 | 2-Phenethyl | H,2-thiazolyl | H | *rac* | 49.53 | 53 | 1.08 |
| 17 | 2-Phenethyl | H,2-fluoroethyl | H | *rac* | 32 | 2.99 | 0.093 |
| 18 | 2-Phenethyl | H,*t*-Bu | H | *rac* | 352 | 608 | 1.73 |
| 19 | 2-Phenethyl | H,phenyl | H | *rac* | 1517 | 4242 | 2.8 |

It is clear that Carson regards compounds **14**, **15**, and **19** as inactive, and compound **15** has an activity of 103 nM. According to Carson compounds with activity of greater than 100nM are inactive. The rather stringent definition of Carson may be debatable, however when comparing the R2 and R3 definitions of the instant case to those of Carson, it is clear that this position profoundly affects the activity. The instant claims exemplify only alkyl and yet are drawn toward a laundry list of "optionally substituted groups".

Morevover in relation to the R1 definition "$C_{2-6}$-heteroaryl" of the instant case to the heteroaryls disclosed by Carson the unpredictable nature of these changes are clear. While Carson show a modest group of "heteroaryls"( indole, pyrrole, thiophene, imidazole, and pyridine), as in Table 1, changes to this group results in large changes in activity. Compare compounds 22 (indole) and compound 27 (pyrrole) to the thiophene derivative 44.

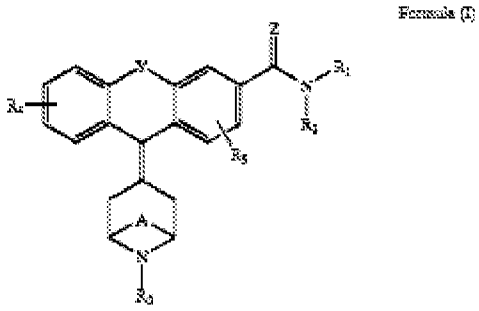
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 22 | 2-(3-Indolyl)-ethyl | R,Et | H | rac | 23.7 | 84 | 3.55 |
| 23 | 5-Methyl-imidazol-4-methyl | R,Et | H | rac | 15.9 | 68 | 3.84 |
| 24 | 2-Hydroxyethyl | R,Et | H | rac | 26.17 | 76 | 2.89 |
| 25 | Imidazol-4-ylmethyl | R,Et | H | rac | 3.88 | 101 | 25.9 |
| 26 | 2-Pyridylmethyl | R,Et | H | rac | 0.80 | 17 | 19.7 |
| 27 | 1-Methylpyrrol-3-yl | R,Et | H | rac | 20.77 | 59 | 2.83 |
| 28 | H | R,Et | 4-OH | rac | 4.5 | 365 | 58.32 |
| 29 | 3,3-Dimethylallyl | R,Et | 3-$CH_3O$ | rac | 0.72 | 2.04 | 2.85 |
| 30 | Allyl | R,Et | 3-$CH_3O$ | rac | 1.45 | 13.8 | 9.54 |
| 31 | H | R,Et | 3-$CH_3O$ | rac | 13.16 | 96.0 | 7.3 |
| 32 | 3,3-Dimethylallyl | R,Et | 3-OH | rac | 2.02 | 2.52 | 1.25 |
| 33 | Allyl | R,Et | 3-OH | rac | 0.264 | 9.56 | 24.94 |
| 34 | 2-Phenethyl | R,Et | 4-$CH_3O$ | rac | 11.29 | 6.1 | 0.54 |
| 35 | 3-Thienylmethyl | R,Et | 4-$CH_3O$ | rac | 1.32 | 13.48 | 10.23 |
| 36 | 2-Chlorobenzyl | R,Et | 4-$CH_3O$ | rac | 5.67 | 122 | 21.63 |
| 37 | 2-Phenethyl | R,Et | 4-OH | rac | 7.8 | 21.7 | 2.79 |
| 38 | 2-Thienylmethyl | R,Et | 4-OH | rac | 0.25 | 6.77 | 27.05 |
| 39 | 3-Chlorobenzyl | R,Et | 4-OH | rac | 0.93 | 8.72 | 9.37 |
| 40 | 2-Phenethyl | R,Et | 3-$CH_3O$ | rac | 19.79 | 0.654 | 0.033 |
| 41 | 2-Thienylmethyl | R,Et | 3-$CH_3O$ | rac | 0.53 | 3.79 | 7.2 |
| 42 | 3-Chlorobenzyl | R,Et | 3-$CH_3O$ | rac | 6.66 | 57.24 | 8.67 |
| 43 | 2-Phenethyl | R,Et | 3-OH | rac | 8.14 | 0.222 | 0.05 |
| 44 | 3-Thienylmethyl | R,Et | 3-OH | rac | 0.152 | 0.664 | 4.37 |
| 45 | 2-Chlorobenzyl | R,Et | 3-OH | rac | 2.09 | 14.88 | 7.12 |
| 46 | $CH_3$ | R,Et | H | 1S,5R | 6.39 | 42.46 | 6.65 |
| 47 | H | R,Et | H | 1S,5R | 5.48 | 74.73 | 13.63 |
| 48 | Allyl | R,Et | H | 1S,5R | 2.24 | 10.52 | 4.69 |
| 49 | $CH_3$ | R,Et | H | 1R,5S | 292 | 304 | 1.04 |
| 50 | Allyl | R,Et | H | 1R,5S | 7.72 | 19.09 | 2.47 |

In terms of the "heteroaryl" substituent of $R^1$, another teaching relevant to the instant case include Coats et. al. "Parallel methods for the preparation and SAR exploration of N-ethyl-4-[(8-alkyl-8-aza-bicyclo[3.2.1]-oct-3-ylidene)-aryl-methyl]-benzamides, powerful mu and delta opioid agonists" *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 5493–5498. Coats et. al. make the following statement with regard to "heteroaryl" substituent of $R^1$:

"Basic groups such as 2-pyridyl (15) and 2-pyrazinyl (16) behaved similarly in the bindingassays. While only 2-furanyl (17) is shown, we found that a broad range of other small heterocycles could effectively replace the olefinic R3 substituent of 3 such as 3-furanyl, 2-thiophenyl, 3-thiophenyl, and 4-isoxazolyl. The R2 substituent of 3 was also tolerant of small heterocyclic groups such as thienyl (14–16) and 4-imidazolo (19). Basic groups in the R2 position generally led to a significant loss in opioid binding; unless matched with an optimal R3 as in the case of 3-pyridyl (21) and 2-pyridyl (22). Groups containingacid functionality attached at R2, as in the case of 18, always led to a significant loss in activity. As was found in related delta opioid agonists15 smaller groups at R2 were optimal while larger groups (not shown) trended toward a loss of opioid binding affinity."

Carson et. al. U.S. PG Pub 2005/009860 A1, who have reported six examples of heteroaryls, namely furan, benzothiophene, isoxazole, quinoline, thiophene, and pyridine,

attached to a core similar to the instant case that are also opioid receptor ligands. The relevant data is show below for convenience:



Formula (I)

10 Table 1

| Cpd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | A | Y | Z |
|---|---|---|---|---|---|---|---|---|
| 85 | Et | Et | H | 7-pyridin-4-yl | H | $CH_2CH_2$ | O | O |
| 86 | Et | Et | H | 7-furan-3-yl | H | $CH_2CH_2$ | O | O |
| 87 | Et | Et | H | 7-benzo thiophen-2-yl | H | $CH_2CH_2$ | O | O |
| 89 | Et | Et | H | 7-pyridin-3-yl | H | $CH_2CH_2$ | O | O |
| 90 | Et | Et | H | 7-thiophen 3-yl | H | $CH_2CH_2$ | O | O |
| 91 | Et | Et | H | 7-(3,5-dimethyl) isoxazol-4-yl | H | $CH_2CH_2$ | O | O |
| 93 | Et | Et | H | 7-pyrrol-2-yl | H | $CH_2CH_2$ | O | O |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 96 | Et | Et | H | 5-pyridin-4-yl | H | $CH_2CH_2$ | O | O |
| 97 | Et | Et | H | 5-furan-3-yl | H | $CH_2CH_2$ | O | O |
| 98 | Et | Et | H | 5-quinolin-3-yl | H | $CH_2CH_2$ | O | O |
| 99 | Et | Et | H | 5-thiophen-3-yl | H | $CH_2CH_2$ | O | O |
| 101 | Et | Et | H | 5-pyridin-3-yl | H | $CH_2CH_2$ | O | O |

Biological and Mass Spectral Data

Table 2

| Cmpd No. | rDOR Ki (nM) | rMOR Ki (nM) | hDOR GTPγS $EC_{50}$(nM) | hMOR GTPγS %I @10μM | DOR GTPγS $EC_{50}$ (nM) | MAIT %I @ 150μmol | Parent Peak obs | MS calcd |
|---|---|---|---|---|---|---|---|---|
| 85 | 3004.5 | 10700 | | | | | 466.1 | 465.60 |
| 86 | 1755 | 12525 | | | | | 455.1 | 454.57 |
| 87 | 12060 | 29025 | | | | | 421.1 | 520.70 |
| 89 | 1953 | 18670 | | | | | 466.2 | 465.60 |
| 90 | 838.15 | 12360 | | | | | 471.1 | 470.64 |
| 91 | 1351.5 | 6702 | | | | | 484.1 | 483.61 |
| 93 | >10000 | >10000 | | | | | 454.4 | 453.59 |
| 96 | 1.692 | 4224 | | | 35.3 | | 466.1 | 465.60 |
| 97 | 1.7785 | 1806 | | | 13.3 | | 455.1 | 454.57 |
| 98 | 24.54 | 7355 | | | | | 516.2 | 515.66 |
| 99 | 18.335 | 3488 | | | 12.5 | | 471.0 | 470.64 |
| 101 | 9.14235 | 532.3 | | | 19.3 | | 466 | 465.60 |

Compound 87 ( $R_4$ is benzothiophene) & 93 ($R_4$ is a pyrrole) are inactive (or at least they don't bind to either receptor tested). The data of Carson et. al. show that identity of the heteroaryl is

important, and upon changing say from a pyridine in compound 96 to a pyrrazole in compound 93 all activity is lost. This is not really surprising, as it is well known that molecular structure is correlated with physical properties and in particular in heterocyclic chemistry the change from one ring to another often results in dramatic changes in properties. Pozharskii et. al. *Heterocycles in Life and Society* Wiley, 1997, pgs. 1-6):

> "It is rumored that the Russian scientist Beketov once compared heterocyclic molecules to jewelry rings studded with precious stones. Several carbon atoms thus make up the setting of the molecular ring, while the role of the jewel is played by an atom of another element, a heteroatom. In general, it is the heteroatom which imparts to a heterocycle its distinctive and sometimes striking properties. ..... the heteroaromatic compounds, as the most important group of heterocycles, possess, highly specific features....."

Given the diverse behavior and complete lack of activity for certain groups, such prophetic recitations as those of the instant claims should be evaluated carefully. In terms of the "heteroaryl" substituent of $R_1$ of the instant case the specification gives only four examples of actual compounds, in terms of the heteroaryl which are furan, thiophene, pyridine and thiazole. Based upon the sheer unpredictability of the area of opioid receptor ligands as evidenced by the prior art, and the paucity of working examples it is readily apparent that one could not make/use this very broad invention without undue experimentation. Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-5, 8, 13, 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 8 of U.S. 6,187,792 in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905 and Iddon et. al. "Acetamides of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (benzomorphan), 5,6.7,8,9,10-hexahydro-6,9-methanobenzocyclo-octene, and 6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[b][1]benzothiophene as potential selective opioid analgesics." *Journal of the Chemical Society Perkin Transaction* 1, **1990**, 1091 -1095 See the 103 (a) rejection supra.

8. Claims 1-5, 8, 13, 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6 of U.S. 6,455,545, in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905. Iddon et. al. "Acetamides of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (benzomorphan), 5,6.7,8,9,10-hexahydro-6,9-methanobenzocyclo-octene, and 6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[b][1]benzothiophene as potential selective opioid analgesics." *Journal of the Chemical Society Perkin Transaction* 1, **1990**, 1091 -1095 See the 103 (a) rejection supra.

9. Claims 1-5, 8, 13, 19-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 13, 19, 22 of U.S. 6,693,117, in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905 Iddon et. al. "Acetamides of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (benzomorphan), 5,6.7,8,9,10-hexahydro-6,9-methanobenzocyclo-octene, and 6,7,8,9,10,11-hexahydro-7,10-methanocyclo-octa[b][1]benzothiophene as potential selective opioid analgesics." *Journal of the Chemical Society Perkin Transaction* 1, **1990**, 1091 -1095 See the 103 (a) rejection supra.

10. Claims 1-5, 8, 13, 19-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 8, 15-18 of copending Application No. 10/596,850, in view of U.S. 6,187,792 and Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905. The claims of the instant case differ from those of the '850 application in the identity of R1. At least where R1 is phenyl or H (Formula III) of the

instant case, the alkyl, cycloalkyl, and H derivatives of the '850 application are equivalents as taught by the secondary references.

This is a provisional obviousness-type double patenting rejection.

11. The examiner notes a very large number of copending commonly assigned applications covering similar subject matter (more than 30) with titles like "therapeutic compounds", "novel compounds" etc. The burden is now shifted to the applicant to point out any more instances of double patenting based on the rational in the 103(a) rejection supra. Please point out any instances of diaphenylmethylene-4-piperdine applications that are pending.

***Conclusion***

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625